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**JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY
ON CHEMICALS**

Task Force on Harmonisation of Classification and Labelling

Ad Hoc Group on Target Organ Toxicity

ISSUE DOCUMENT No 1: SINGLE, PROLONGED OR CHRONIC EXPOSURE

**2nd Meeting of the ad hoc Expert Group on Target Organ Toxicity,
9th-10th September 1999, Bethesda, Maryland, beginning at 9:30 on 9th September**

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ISSUE DOCUMENT NO 1: SINGLE, PROLONGED OR CHRONIC EXPOSURE

ISSUE

1. Should the toxicologically significant effects that occur from single, prolonged or chronic exposures be included in target organ toxicity? Or include only effects from prolonged or chronic exposures.

CURRENT PRACTICE

Canada

WHMIS

2. The Canadian workplace system includes adverse effects which develop over time following a single exposure to a substance or from prolonged or repeated exposure to a substance under conditions that do not produce that effect from a single exposure.

EU

3. Includes effects from single, prolonged or repeated exposures.
4. The EU classification end-point for 'repeated-dose toxicity' is concerned with substances that cause serious damage to human health resulting from prolonged exposure. Serious damage to health in this context refers to death, toxicologically significant clear functional disturbance or morphological change that is caused by repeated or prolonged exposure by an appropriate route. It is particularly important when these changes are irreversible.

US

OSHA

5. Chronic effects resulting from long term exposure are included.

Consumer Products:

6. Includes effects from single, prolonged or repeated exposures.

Pesticides

7. Effects from single or multiple exposures are included.

OPTIONS

Include toxicologically significant effects from single, prolonged and chronic exposures.

8. Existing systems except for the workers in US currently include classification/identification of hazards from single, prolonged or chronic exposures. The health hazard from single exposure is generally based on human data. Currently none of the systems have criteria to use the effects observed in acute toxicity studies that are prolonged and or severe but do not lead to mortality. However, the EU system provides for classification of very serious (non-lethal) irreversible effects, or irreversible (non-lethal) effects that result from acute, ie. single exposure. Usually these effects reoccur in repeat dose studies and

are then used. The objective of GHS is to identify and classify all hazards posed by chemicals without reference to extent or degree of exposure. The toxic effects occurring from single exposure that do not lead to mortality in animals have not been covered so far. These effects are generally organ specific and this is the most appropriate place to include them as required by many systems.

Include toxic hazards observed only from prolonged and chronic exposures and exclude those from single or acute exposures

Comment (from Derek James)

9. Methanol is a rare case for serious non-lethal health consequence following a single exposure. There are very few chemicals (probably less than 8) known to produce such effects. The classification of methanol for this effect is based on evidence from human experience rather than from animal studies, and the effect is produced by exposure to significant (ie. high) concentration. It has therefore been treated as a special case. Available data does not normally permit distinction between long term effects caused by a single exposure or repeated dose exposure. There is no current recognised protocol to reveal such long-term effects resulting from a single exposure. And it is difficult enough to identify the causative chemical factor of an effect observed in humans following repeated dose exposure; to identify such an effect following a single exposure in humans would be virtually impossible in view of the daily exposure to a variety of other chemicals (which one caused the effect ?, and when was the effect initiated ?) in the intervening period between the single exposure and the eventual observed effect.

10. Only in cases of major accident (usually to very high concentration) do we stand a reasonable chance of making a clear positive connection between a single (high dose ?) exposure and a serious health outcome.

11. Consider the objective of the current classification end-point; it is to be able to warn people about the health hazards associated with repeated or long-term exposure, normally to relatively low concentrations. This is because people are expected to be exposed repeatedly, often daily, to some concentration of the chemical in question - and so by knowing the health hazards associated with this situation appropriate measures can be recommended and taken in order to control the risks to health. This holds for the workplace, eg. solvents, polymerisers, plasticisers, etc., and also for consumers, eg. detergents, paints, polishes, etc. The information required to assess this type of hazard comes from studies of repeated exposure to relatively low concentrations, either from epidemiology studies (which provide very limited information and are often not very reliable) or from standardised repeated-dose studies in animals with a very detailed macroscopic and microscopic examination at termination to enable the toxic effects (usually non-lethal), especially on target organs, to be identified. By contrast, dangerous consequences following single dose exposure are to be considered much more seriously, so that even single-time exposure is to be avoided. This represents a different objective, and therefore a different end-point and different information (usually causing death) from different test methods, using relatively high doses, in order to identify the hazard.

12. One could argue that if a chemical is acutely toxic it is not necessary to test for repeated-dose toxicity at all because it is known already to be toxic. Long term effects resulting from single dose exposure are dealt with under the end-point for Acute toxicity (or might be). The end-point for Systemic toxicity (target organ oriented toxicity) addresses only the hazardous consequences of repeated-dose exposure.